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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/782,570
Filing Date: February 19, 2004
Appellant(s): CAROZZI ET AL.

Destiny M. Davenport
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 17 October 2011 appealing from the Office action mailed 18 May 2011

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Application Nos. 10/782,096, 10/782,141, and 10/783,417 (each filed February 19, 2004)

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-11, 19, 22-23 and 30

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

US 5,625,136	Koziel et al	1997
US 6,156,308	Liu et al	2000

Ben-Dov et al (1996, Appl. Environ. Microbiol., 62:3140-3145)

Carlton et al (1985, Mol. Biol. Microb. Differ., Proc. Intl. Spore Conf., 9th, Meeting date 1984, pages 246-252; Ed. Hoch et al, Am.Soc. Microbiol., Washington, DC)

deMaagd et al (2001, Trends. Genet. 17:193-199)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. Claims 1 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al (1996, Appl. Environ. Microbiol., 62:3140-3145) in view of Liu et al (2000, US Patent 6,156,308) and further in view of Carlton et al (1985, Mol. Biol. Microb. Differ., Proc. Intl. Spore Conf., 9th, Meeting date 1984, pages 246-252; Ed. Hoch et al, Am.Soc. Microbiol., Washington, DC) and further in view of deMaagd et al (2001, Trends. Genet. 17:193-199) and taken with the evidence of Appellant's response to the Request for Information under 37 CFR 1.105.

Appellant's response to the Request for Information under 37 CFR 1.105, filed 17 March 2009, indicates that the bacterial strain from which SEQ ID NO:1-4 were isolated is HD536, and available from the USDA.

The claims are drawn to a nucleic acid encoding a toxin comprising SEQ ID NO:2 or 4; both of these toxins comprise SEQ ID NO:4.

Ben-Dov et al teach restriction mapping of a *Bacillus thuringiensis* plasmid (pg 3141, left column, to pg 3143, right column, 3). The method involved isolating the plasmid DNA (pg 3140, right column, ¶4), cloning fragments in vectors that encode a selectable-marker protein heterologous to the endotoxin, and growing these clones in an *E. coli* host cell (pg 3140, right column, ¶2; pg 3143, right column, ¶2); using the fragments in restriction mapping (pg 3141, left column, to pg 3143, right column, 3). Ben-Dov et al do not teach a nucleic acid encoding SEQ ID NO:2 or 4.

Liu et al teach that it would be advantageous to isolate new *B. thuringiensis* toxins to increase the spectrum of biopesticides (column 3, lines 6-8). Liu et al also teach a method of isolating *B. thuringiensis* toxin genes, involving sequencing the proteins from the toxin crystals,

using them to make probes, using the probes to isolate the genes encoding the toxins, and sequencing the genes (column 15, line 19, to column 17, line 25). Liu et al also teach expressing the toxins in heterologous bacteria (column 6, line 25, to column 7, line 31).

Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production (Table 1).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to clone delta-endotoxin genes from strain HD536 described in Carlton et al using the methods described in Ben-Dov et al and Liu et al. One of ordinary skill in the art would have sequenced the plasmid fragments, translate the resulting sequences to identify open reading frames; comparison to known Cry protein conserved sequence and structural domains, as taught by deMaagd et al (paragraph spanning pg 193-194; Fig. 2), would aid in identifying Cry-encoding reading frames. Further, use of probes made by the method Liu et al and designed from the protein sequences of toxins made by HD536 would have aided in cloning toxin genes, including those encoding SEQ ID NO:2 or 4, from that strain. The level of ordinary skill in this art is very high, as evidenced by each of Ben-Dov et al, Liu et al, and deMaagd et al.

One of ordinary skill in the art would have been motivated to do this cloning because an increased repertoire of delta-endotoxins would be desirable for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins.

It would be obvious to one of ordinary skill in the art to use the 68 MDa plasmid from HD536 because HD536 was known in the art as having a toxin-encoding plasmid (Carlton et al,

Table 1). In cloning the toxins from the 68 MDa plasmid from HD536, one of skill in the art would necessarily isolate a nucleic acid encoding SEQ ID NO:2 or 4.

It would be obvious to one of skill in the art to culture the host cell comprising the plasmid in conditions under which the nucleic acid encoding the toxins is expressed to study the toxicity of the protein, particularly for toxicity to lepidopteran plant pests, and to produce large quantities of the toxin, as suggested by Liu et al (column 6, lines 25-36).

B. Claims 2-3, 8-11, 19, 22-23 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al as applied to claims 1 and 4-7 above, and further in view of Koziel et al (1997, US Patent 5,625,136).

The claims are drawn to plants transformed with a nucleic acid encoding a toxin comprising SEQ ID NO:2 or 4, including plant optimized nucleic acids.

The teachings of Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al are discussed above. Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al do not teach plants and seeds transformed with the nucleic acid.

The teachings of Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al are discussed above. Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al do not teach plants and seeds transformed with the nucleic acid.

Koziel et al teach construction of a Cry endotoxin coding sequence that is designed for expression in a plant; this sequence has increased GC content relative to the native coding sequence (column 7, lines 19-56; column 9, lines 50-56). Koziel et al also teach expression of the modified Cry endotoxin coding sequence in maize cells from a vector that also encodes phosphoenolpyrivate carboxylase (column 59, line 40, to column 63, line 50), as well as maize plants and seeds transformed with the modified Cry endotoxin coding sequence (claims 4-25).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to operably link the nucleic acid made obvious by Ben-Dov et al in view of Liu et al and further in view of Carlton et al and further in view of deMaagd et al to a plant promoter and transform the resulting construct into plants, including maize, as described in Koziel et al. One of ordinary skill in the art would have been motivated to do so because the resultant plants will be more resistant to insect pests and the farmer thus less likely to suffer economic loss because of them. Further, Lui et al also suggest expressing the toxins in plants (column 7, lines 32-38).

(10) Response to Argument

One of skill in the art would be motivated to combine Ben-Dov et al with Liu et al, Carlton et al, and deMaagd et al

Appellant urges that the examiner impermissibly uses Appellant's specification as a basis for the rejection; outside of Appellant's specification one of ordinary skill in the art would have no reason to use HD536 given the numerous other strains having insecticidal activity (Brief pg 4-5).

However, Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production (Table 1). Carlton et al teach a finite number of such strains, 17. The motivation for using strains known to produce toxins rather ones not so known is that one of skill in the art would know that cloning from a toxin-encoding strain would have a reasonable expectation of success. That Appellant has renamed the strain does not make it nonobvious to use, given Carlton et al's teachings.

Appellant urges that Ben-Dov et al teach cloning large restriction fragments from a single 125 kB plasmid and using probe specific for known toxins (Brief pg 5).

However, the rejection is not over Ben-Dov et al alone, but is based on a combination of references. Liu et al teach cloning and sequencing genes; their method involves sequencing the proteins from the toxin crystals, using them to make probes, using the probes to isolate the genes encoding the toxins, and sequencing the genes (column 15, line 19, to column 17, line 25). In combination with the methods taught in Ben-Dov et al, one of ordinary skill in the art would have sequenced the plasmid fragments, translated the resulting sequences to identify open reading frames and compared them to known Cry protein conserved sequence and structural domains to aid in identifying Cry encoding reading frames, as taught by deMaagd et al.

Appellant urges that Carlton et al fails to make up for the deficiencies of Ben-Dov et al; Carlton et al provides a laundry list of plasmids (Brief pg 5).

However, Ben-Dov et al and Liu et al teach cloning and sequencing genes. Carlton et al points to a starting Bacillus strain, with a plasmid smaller than used in Ben-Dov et al, to use in cloning toxins. Carlton et al's list is of a mere 17 strains, not a large number.

Appellant urges that Lui et al fail to make up for the deficiencies of Ben-Dov et al; Lui et al could not isolate genes using PCR and had to partially sequence protein bands fractionated from these isolate. One of skill in the art would be unlikely to use the methods of Lui to identify every single gene on HD536 (Brief pg 6).

However, Lui et al teach additional methods for cloning Bacillus toxins; one of skill in the art would use partial sequencing of protein bands fractionated from the isolate to make probes for cloning. Restriction mapping of the 68 MDa plasmid in HD536 and subsequent sequencing of the fragments, would result in isolation of SEQ ID NO:1 and 3. Thus, there was a reasonable expectation of success of identifying the specific genes claimed in the instant application.

Appellant urges that one of ordinary skill in the art would have no motivation to combine Ben-Dov, Liu et al and Carlton et al; Ben-Dov uses probes that hybridize to mosquito toxins, and there is no motivation to apply this methodology to other toxins (Brief pg 6).

However, the level of ordinary skill in this art is very high, as evidenced by each of Ben-Dov et al, Liu et al, and deMaagd et al. Use of Ben-Dov's probes would not be necessary, as Liu et al teach making probes designed from the protein sequences of toxins encoded by a bacterial strain. The motivation to apply this methodology to other toxins comes from a desire to have an increased repertoire of delta-endotoxins for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins. There is no reason one of ordinary skill in the art would think that these methods could not be applied to non-mosquito toxins.

Appellant urges that Ben-Dov et al used hybridization methods based on known genes, and only very similar genes were found (Brief pg 6-7).

However, the rejection does not rely solely on Ben-Dov et al' s probes and methods, but also uses Lui et al's methods; Lui et al teach how to make probes based on the proteins actually found in a particular Bacillus strain. Thus, genes with low homology to known proteins can be found.

Appellant urges that Lui et al used probes specific for known toxins to profile two Bacillus strains, and sequenced proteins from toxin crystals and used that information to generate probes; thus one of skill in the art could only identify already known genes or those that encode highly expressed proteins (Brief pg 7).

However, one of ordinary skill in the art would use Lui et al's method of sequencing proteins from toxin crystals to generate probes to clone genes as taught in Lui et al and ben-Dov et al. The use of probes specific to known cry genes is not required.

Appellant has provided no evidence that SEQ ID NO:1 (which comprises SEQ ID NO:3) is a lower-expressed gene. Thus, there was a reasonable expectation of success of identifying the specific genes claimed in the instant application.

One of skill in the would use probes made by the method taught by Lui et al

Appellant urges that one of skill in the art would have no motivation to use Ben-Dov's probes; the claimed sequences have low sequence homology to other known toxins, including the probes used by Ben-Dov (Brief pg 7-8).

However, use of Ben-Dov's probes would not be necessary, as Liu et al teach making probes designed from the protein sequences of toxins encoded by a bacterial strain. The motivation to apply this methodology to other toxins comes from a desire to have an increased repertoire of delta-endotoxins for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), and for overcoming pest resistance to existing endotoxins.

One of skill in the art would be motivated to isolate toxins from Carlton's HD536

Appellant urges that one of ordinary skill in the art would have no motivation to isolate the claimed sequences from HD536 of Carlton et al; HD536 is only one strain in a list and Carlton et al does not specifically indicate why it would be advantageous to isolate sequences from this strain, citing *KSR* (Brief pg 8).

However, Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production. This is one of only 17 such strains that Carlton teaches. Appellant has provided no support for their assertion that no insecticidal activity was demonstrated for this strain prior to their disclosure; such support is required *given Carlton's teaching of toxin production from this strain.*

Carlton et al's teaching of a mere 17 strains that produce toxins is far fewer than the 53 pharmaceutically acceptable salts found to be a finite number in *Pfizer Inc. v. Apotex Inc.,* 82 USPQ2d 1852 (Fed. Cir. 2007). It would advantageous to isolate sequences from this strain because it was known in the art to produce toxins.

See *KSR International Co. v. Teleflex Inc.,* for the proposition that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified

predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 127 S. Ct. 1727, 1732, 82 USPQ 2d 1385, 1397 (2007).

Appellant urges that outside of a loose correlation between the 68 MDa plasmid and toxin production, Carlton fails to suggest that genes from HD536 would have insecticidal activity (Brief pg 8-9).

However, Carlton et al's discussion or toxins is in the context of bioinsecticides (pg 246, left column, paragraph 1). One of ordinary skill in the art would reasonable conclude that the toxins were bioinsecticides.

Appellant urges that in *Eisai* there was no reason to make the substitution because there was no reason to make the particular modifications claimed to the lead compound (Brief pg 9).

However, the case is not analogous, as no modifications were made to any compound. The HD536 68 kDa plasmid is necessary to achieve the claimed molecule; all that is required is sequencing the plasmid. As discussed above, there Carlton taught a finite number of toxin-producing strains; the need for additional toxins provided the motivation to isolate the toxins-encoding genes from those strains.

There is no teaching in the art that HD536 is not insecticidal towards Lygus lineolaris

Appellant urges that AXMI-007 unexpectedly exhibits insecticidal activity against *Lygus lineolaris* (Brief pg 10).

However, Appellant has not shown that the toxin provides activity previously shown not to be present in HD536 or present on the 68 kDa plasmid. There is no teaching, for example, that HD536 was not toxic to *L. lineolaris*. Thus, this activity cannot be unexpected. It is unclear

why the low homology of AXMI-007 to other toxins would make toxicity to *L. lineolaris* unpredictable, especially if these toxins were not known to be toxic to *L. lineolaris*.

One of skill in the art would be motivated to combine Ben-Dov et al with Liu et al, Carlton et al, deMaagd et al and Koziel et al

Appellant urges that there is no motivation to transform the nucleic acids into plant or cells; Ben-Dov has no association with plants, as they were concerned with mosquito toxins and motivation is not found in Carlton (Brief pg 11-12).

However, the level of ordinary skill in this art is very high, as evidenced by each of Ben-Dov et al, Liu et al, and deMaagd et al. Use of Ben-Dov's probes would not be necessary, as Liu et al teach making probes designed from the protein sequences of toxins encoded by a bacterial strain. The motivation to apply this methodology to other toxins comes from a desire to have an increased repertoire of delta-endotoxins for increasing toxicity spectra, as taught by Liu et al (column 3, lines 6-8), for expressing the toxins in plants (Lui et al, column 7, lines 32-38), and for overcoming pest resistance to existing endotoxins.

Appellant could have overcome these rejections by at least any of the following methods: a) showing that HD536 was not toxic to *L. lineolaris*; b) showing that prior to their disclosure HD536 was not known to produce insecticidal toxins; and/or c) showing that HD536 does not produce SEQ ID NO:2/4 at sufficient levels for protein sequencing and for generating probes as in Lui et al. Appellant has not provided evidence of any of these and, thus, has not overcome these rejections.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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